2.0 SYNOPSIS

Name of Sponsor: Hospira, Inc.

Name of Finished Product: Precedex™ (dexmedetomidine hydrochloride) Injection

Name of Active Ingredient: Dexmedetomidine hydrochloride injection

Title of Study: A Phase II, Randomized, Open-Label, Single Center, Pharmacokinetic and Pharmacodynamic Study of Dexmedetomidine in Pediatric Subjects Aged 12 months through < 24 months

Investigators and Study Centers: Constantinos Chrysostomou
Children's Hospital of Pittsburgh of UPMC
Pittsburgh, PA 15224

Publication (reference): Not applicable

Study Period: 23 June 2011 (date of first informed consent) to 04 August 2011

Phase of Development: Phase II

Objectives:

The primary objectives of this study were:

1. To define the pharmacokinetic (PK) profile of dexmedetomidine (DEX) administered as an intravenous (IV) loading dose followed by a continuous IV infusion in pediatric subjects 12 months through < 24 months of age.
2. To define the pharmacodynamic (PD) profile of DEX administered as an IV loading dose followed by a continuous IV infusion in pediatric subjects 12 months through < 24 months of age.

The secondary objective of this study was:

1. To evaluate the safety of DEX in subjects 12 months through < 24 months of age.

Methodology: This was a Phase II open-label, single center, PK, and PD study. Subjects were randomly assigned into 1 of 2 dose levels: dose level 1 consisted of a 0.7 mcg/kg loading dose immediately followed by a 0.5 mcg/kg/hr maintenance infusion; dose level 2 consisted of a 1 mcg/kg loading dose immediately followed by a 0.75 mcg/kg/hr maintenance infusion. The DEX infusion (loading dose and maintenance dose) continued for a minimum of 6 hours but did not exceed 24 hours, including the loading dose time. Titration of dosing was not allowed.

Dose Level	Loading Dose (mcg/kg)	Maintenance Dose (mcg/kg/hour, as a continuous infusion)
1	0.7	0.5
2	1	0.75

Number of Subjects:

Planned: An estimated 6 subjects were to be enrolled in the study: 3 subjects in each dose level.

Enrolled: A total of 5 subjects were randomized, received DEX, and completed the treatment: 2 subjects in dose level 1 and 3 subjects in dose level 2.

Analyzed: The Full Evaluable (FE) Population consisted of all subjects who received study drug for at least 5 hours with adequate PK samples to estimate primary parameters. All PK and PD assessments were conducted primarily on the FE Population. The Safety Evaluable (SE) Population consisted of all subjects who received any amount of study drug. All safety analyses were performed on the SE Population. All 5 subjects who were randomized were included in both the FE and SE Populations.

Diagnosis and Main Criteria for Eligibility: Intubated and mechanically ventilated pediatric subjects between 12 to 24 months of age in an intensive care setting who were anticipated to require a minimum of 6 hours of continuous IV sedation. Serum creatinine at the time of enrollment had to be ≤ 1 mg/dL.

Test Product, Dose and Mode of Administration, Batch Number or Test Device: The loading and maintenance doses of DEX were diluted in 0.9% sodium chloride or dextrose 5% in water (D5W) to 4 mcg/mL.

Batch Number: 95-261-DK

Duration of Treatment: Study drug administration, consisting of a loading dose and a maintenance dose continuous infusion could be administered for a minimum of 6 but not more than 24 hours in duration.

Reference Therapy, Dose and Mode of Administration, Batch Number: None

Criteria for Evaluation:

Pharmacokinetic Assessments:
The PK parameters of DEX that were calculated included:

- Area under the concentration-time curve (AUC)
- Observed peak plasma concentration (C_{max})
- Steady state concentration at (C_{ss})
- Plasma clearance (CL)
- Terminal-phase elimination rate constant (λz)
- Observed time to reach maximum plasma concentration, expressed in hours (T_{max})
- Terminal elimination half-life ($t_{1/2}$)
- Volume of distribution (V_d)
- Volume of distribution at steady state (V_{ss})

Additional parameters were assessed, as deemed appropriate.

Pharmacodynamic Assessments:

- Use of rescue medication (midazolam [MDZ] or fentanyl)
- Level of sedation according to the University of Michigan Sedation Scale (UMSS)
- Pain scores from the Face, Legs, Activity, Cry, and Consolability (FLACC) tool
- Time to first dose of rescue medication for sedation and analgesia
- Vital signs, i.e., heart rate (HR), SBP (systolic blood pressure), DBP (diastolic blood pressure), mean arterial pressure (MAP), respiratory rate (RR), and oxygen saturation by pulse oximetry (SpO_2)
- Time to extubation

Safety Assessments:

- Exposure to DEX
- Adverse events (AEs)
- Clinical laboratory tests (hematology, chemistry [including liver function], and urinalysis)
- Physical examinations
- Vital signs (see PD assessments above)
- Withdrawal such as changes in HR or blood pressure (after discontinuation of DEX infusion)
- Input/output fluid volume
- Electrocardiograms (ECGs)

Statistical Methods: The statistical analyses were performed using SAS, version 9.1. Descriptive statistics were primarily used.

SUMMARY

PHARMACOKINETIC RESULTS:

- T_{max} was generally 0.08 hrs before the end of the loading dose, and was fairly constant across all subjects and dose groups.
- Exposure to DEX, measured as C_{max} or AUC, appeared to be dose-related.
- Dexmedetomidine $t_{1/2}$ was about 2 hrs in all subjects and was independent of dose.
- Both CL and V_d were independent of dose.

PHARMACODYNAMIC RESULTS:

- The maintenance infusion doses of DEX used in this trial, 0.5 mcg/kg/hr (dose level 1) and 0.75 mcg/kg/hr (dose level 2), were moderately effective at sedating and keeping subjects comfortable. The use of concomitant sedatives and analgesics confounded the interpretation of the PD results.
- Compared to dose level 2 subjects, subjects in dose level 1 spent considerably less time in the target UMSS range of 2 to 4, but had lower total FLACC scores.
- Generally, trends in mean change from baseline in vital signs were not clinically meaningful.

SAFETY RESULTS:

- Dexmedetomidine was safe and well tolerated at both dose levels.
- Only 1 of the 5 subjects (20.0%) experienced TEAEs. These events were mild pyrexia and mild atelectasis in a dose level 2 subject; both events were assessed as not related to DEX. There were no treatment-emergent SAEs leading to death, no other treatment-emergent SAEs, and no TEAEs that led to DEX discontinuation.
- There were no hematology, chemistry, or urinalysis values assessed as clinically significant or as TEAEs by the Investigator.
- In general, changes from baseline were not clinically meaningful for vital signs or physical examination data.
- No abnormal clinically significant ECG findings were present in any of the 5 study subjects at screening or during or post-DEX administration.

CONCLUSIONS: Dexmedetomidine exhibited linear pharmacokinetics across the doses of 0.5 mcg/kg/hr (dose level 1) and 0.75 mcg/kg/hr (dose level 2). T_{max}, dose adjusted C_{max} and AUC (0-Infinity), $t_{1/2}$, CL, and V_d were all independent of dose. Due to a high degree of variability, there was no clear relationship between PK parameters ($C_{max,}$ AUC, CL, or V_d) and age across subjects.

The maintenance infusion doses of DEX used in this trial, 0.5 mcg/kg/hr (dose level 1) and 0.75 mcg/kg/hr (dose level 2), were moderately effective at sedating and keeping subjects comfortable. The use of concomitant sedatives and analgesics confounded the interpretation of the PD results. Compared to dose level 2 subjects, subjects in dose level 1 spent less considerably less time in the target UMSS range of 2 to 4, but had lower total FLACC scores. Dexmedetomidine was safe and well tolerated at both dose levels.

Date of the report: 26 August 2011